SYNTHESIS OF QUINOLIZINE DERIVATIVES
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POLYCYCLIC STRUCTURES INCORPORATING THE quinolizine RING SYSTEM ARE PRESENT IN BERBERINE AND RELATED ALKALOIDS. AN INGENIOUS METHOD FOR THE SYNTHESIS OF SUCH TYPES OF BENZO- AND DIBENZOQUINOLIZINES WAS DEVELOPED BY Sugasawa AND SUGIMOTO. THIS CONSISTS IN THE OXIDATION BY ALKALINE FERRICAMIDE OF A QUATERNARY SALT FORMED BETWEEN A PHENYL ETHYL HALIDE AND A HETEROCYCLIC BASE, TO THE CYCLIC AMIDE, FOLLOWED BY THE CYCLISATION OF THE LATTER WITH PHOSPHOROUS OXYCHLORIDE TO A QUINOLIZINE HALIDE. THE METHOD HAS BEEN SUCCESSFULLY APPLIED FOR THE SYNTHESIS OF ANALOGUES OF EMETINE. HOWEVER, ONLY ALKXY SUBSTITUTED PHENYL ETHYL HALIDES AND SIMILARLY SUBSTITUTED HETEROCYCLIC BASES HAVE SO FAR BEEN USED IN THIS METHOD PROBABLY DUE TO THE BELIEF THAT IN THE ABSENCE OF SUCH ALKXY SUBSTITUTION, RING CLOSURE MAY NOT PROCEED AT ALL. INDEED EVEN THOUGH THE SIMPLE N \( \beta \)-PHENETHYL-2-PYRIDONE AND N-\( \beta \)-PHENETHYL-2-QUINOLINE HAD BEEN MADE BY Sugasawa AND SUGIMOTO, NO ATTEMPTS WERE MADE TO CYCLE THEM TO THE CORRESPONDING QUINOLIZINES.

The object of the study presented in this paper was to ascertain whether benzo- and dibenzoquinolizines could be synthesised by the Sugasawa procedure in the absence of activating alkxy substitutes. QUATERNARY SALTS WERE FORMED BETWEEN \( \beta \)-PHENETHYL BROMIDE AND PYRIDINE, \( \alpha \)-Picoline, quinoline and isoquinoline. THESE BROMIDES HAVE BEEN REPORTED PREVIOUSLY. QUATERNARY SALTS WERE ALSO FORMED BETWEEN \( \beta \)-NAPHTHYL ETHYL BROMIDE AND PYRIDINE, QUINOLINE, 4 METHYL QUINOLINE, 7 METHYL QUINOLINE AND ISOQUINOLINE. THESE SALTS HAVE NOT BEEN REPORTED BEFORE. THEY WERE CRYSTALLINE SOLIDS, SPARINGLY SOLUBLE IN WATER AND NOT AT ALL HYDROSCOPIC UNLIKE THE QUATERNARY SALTS WITH \( \beta \)-PHENETHYL BROMIDE.

The oxidation of these quaternary salts was generally conducted at room temperature with alkaline potassium ferricyanide \( \text{N}-\beta \)-Phenethyl-4-picolinium bromide, \( \text{N}-\beta \)-Phenethyl quinolinium bromide and \( \text{N}-\beta \)-1-naphtyl) ethyl lepidinium bromide gave on oxidation only tarry oils under a variety of conditions. It was possible however to isolate the expected *THE MATERIAL EMBODIED IN THIS PAPER FORMED PART OF A THESIS SUBMITTED TO THE UNIVERSITY OF MADRAS IN JANUARY 1951 FOR THE DEGREE OF MASTER OF SCIENCE. WHILE THE PAPER WAS IN PREPARATION ATTENTION HAS BEEN DRAWN TO A PUBLICATION BY Sugasawa et al. IN THE J. Pharm. Soc. Jap., 72, No. 10, p. 1275, IN WHICH THE SYNTHESIS OF THREE OF THE COMPOUNDS PREPARED BY US IN THE COURSE OF THIS STUDY ARE REPORTED.
oxidation product in crystalline condition by chromatographic fractionation of the tarry products, though in poor yields. The other quarternary salts were converted to the cyclic amides in excellent yield by oxidation with alkaline ferricyanide.

With the exception of N-β-phenethyl-6-methyl-2-pyridone, N-β-phenethyl-2-quinolone and N-β-(1-naphthyl) ethyl-4-methyl-2-quinolone, which were obtained in low yields, all the other cyclic amides were cyclised to the substituted quinolinium salts by the action of phosphorous oxychloride and isolated as the quarternary iodides. The cyclisations have been found to proceed in excellent yields in all cases.

This remarkable ease of cyclisation is in striking contrast to the difficulty of cyclisation of acyl derivatives of β-phenethyl amine. The driving force in the present case appears to be the tendency of the heterocyclic part of the molecule to become fully aromatic.

The various quinolizinium iodides were reduced smoothly to the corresponding hydroquinolizines by reduction in alcohol medium in the presence of Adams’ catalyst. The reduction products were purified by chromatography and characterised as hydrochlorides, picrates or picrolonates.

**Experimental**

β-phenethyl bromide was made by the method of Rupe.

β-1-naphthyl ethyl bromide was made by the method of Haworth and Mavin.

N-β-phenethyl pyridinium bromide

Pyridine (5 g.) and β-phenethyl bromide (10 g.) were refluxed in dry toluene (50 ml.) for three hours. A white crystalline solid separated on cooling. It was filtered and washed with absolute ether. On recrystallisation from absolute alcohol-ether mixture it was obtained in the form of lustrous needles melting at 125–126°; yield, 14.5 g. (Found: N, 5.5%; C_{13}H_{14}NBr requires N, 5.3%).
Sugasawa and Sugimoto\textsuperscript{1} report the melting point of this compound as 112\degree.

**N-β-phenethyl pyridinium iodide**

A solution of N-β-phenethyl pyridinium bromide (0.5 g.) in water (5 ml.) was treated with a saturated aqueous solution of potassium iodide (5 ml.). The precipitated iodide was crystallised from a mixture of absolute alcohol and ether and was obtained in the form of glistening needles melting at 166\degree (Found: N, 4.7%; \( \text{C}_{13}\text{H}_{14}\text{NI} \) requires N, 4.5%).

**N-β-phenethyl-2-pyridone**

A solution of N-β-phenethyl pyridinium bromide (2.6 g.) in water (25 ml.) was added dropwise to a vigorously stirred aqueous solution of potassium ferricyanide (11.8 g.) and sodium hydroxide (3 g.) in the minimum amount of water. The solution was stirred for six hours at room temperature. The brown solid which separated was filtered, washed with water, dried and recrystallised from benzene, yielding colourless plates melting at 105\degree. The aqueous filtrate on extraction with benzene gave a small amount of the same pyridone. Yield, 1.3 g. (Found: C, 78.1%; H, 6.5%; N, 7.4%; \( \text{C}_{13}\text{H}_{13}\text{NO} \) requires C, 78.4%; H, 6.5%; N, 7.0%).

**3: 4-dihydro-9: 10-dehydro-1: 2-benzoquinolizinium iodide**

A solution of the above pyridone (1.5 g.) in absolute benzene (25 ml.) was refluxed with phosphorous oxychloride (12 ml.) for three hours. The reaction mixture was cooled and treated with a large excess of petroleum ether (b.p. 40–60\degree). After an hour, the solvent was decanted off from the black oil which had settled at the bottom. The oil was dissolved in dilute hydrochloric acid (0.2N, 25 ml.), warmed and filtered. The clear filtrate was treated with excess of a saturated aqueous solution of potassium iodide. The precipitated product was filtered, washed with water, dried and recrystallised from alcohol, when it was obtained as a fine yellow powdery material melting at 190\degree; yield, 1.9 g. (Found: C, 50.1%; H, 3.6%; N, 4.6%; \( \text{C}_{13}\text{H}_{12}\text{NI} \) requires C, 50.5%; H, 3.9%; N, 4.5%).

**3: 4: 5: 6: 7: 8-hexahydro-1: 2-benzoquinolizine**

A solution of the above benzoquinolizinium iodide (0.5 g.) in alcohol (100 ml.) was shaken with hydrogen at a pressure of 60 lb./sq. in. in the presence of Adams’ catalyst (0.1 g.). When the absorption of hydrogen ceased, the solution was filtered to remove the catalyst and the filtrate distilled off to remove the solvent. The residue was dissolved in water and made alkaline. The liberated base was extracted with ether. On removal
of the solvent a reddish oil was obtained which could not be induced to solidify.

The picrate prepared in the usual way from this oil was recrystallised from alcohol when it was obtained in the form of yellow prisms melting at 123° (Found: C, 54·1%; H, 8·0%; N, 13·8%; \( \text{C}_{15}\text{H}_{23}\text{N}_{2}\text{O}_6 \) requires C, 54·7%; H, 8·0%; N, 13·4%).

The picrolonate prepared by mixing alcoholic solutions of the oil and picrolonate and was crystallised from alcohol when it was obtained in the form of yellow needles melting at 208° (Found: C, 60·8%; H, 5·6%; N, 15·6%; \( \text{C}_{15}\text{H}_{23}\text{N}_{2}\text{O}_5 \) requires C, 61·4%; H, 5·8%; N, 15·5%).

The following compounds were prepared by methods analogous to those described above.

3:4:5:6-tetrahydro-1,2,3-sulphenzoquinolizine

\( N^{\beta}-\text{phenethyl quinolinolizinium bromide} \) It was crystallised from a mixture of absolute alcohol and ether and was obtained in the form of shining needles melting at 133° (Found: N, 4·8%; \( \text{C}_{15}\text{H}_{16}\text{NBr} \) requires N, 4·5%). \( N^{\beta}-\text{phenethyl quinolinolizinium iodide} \) was crystallised from alcohol when it was obtained in the form of colourless needles melting at 177° (Found: N, 4·0%; \( \text{C}_{15}\text{H}_{14}\text{NI} \) requires N, 4·9%). \( N^{\beta}-\text{phenethyl quinolinolizine-1 was obtained by oxidation of the quaternary bromide with alkaline ferricyanide. Crystallisation from benzene gave pale yellow plates melting at 102°. 3 g. of the quaternary bromide yielded 2·1 g. of the quinolinolizine (Found: C, 82·2%; H, 6·2%; N, 8·9%; \( \text{C}_{15}\text{H}_{14}\text{NO} \) requires C, 81·9%; H, 6·0%; N, 8·6%). 3:4:5:6-tetrahydro-1,2,3,4,5,6,7-sulphenzoquinolizinium iodide, obtained by the cyclisation of the above quinolinolizine was recrystallised from water. It separated as yellow needles melting at 120°. After drying at 100° for three hours in vacuo it melted at 188°. 2·2 g. of the quinolinolizinium iodide (Found: C, 56·6%; H, 3·8%; N, 4·1%; \( \text{C}_{15}\text{H}_{14}\text{NI} \) requires C, 56·8%; H, 3·9%; N, 4·0%).

3:4:5:6-tetrahydro-1,2,3-sulphenzoquinolizine was obtained by catalytic reduction of the above iodide and was obtained in the form of an oil. When the oil was treated with hydrochloric acid and the hydrochloride was formed which on recrystallisation from dilute alcohol was obtained as a fine powder, melting at 201° (Found: C, 54·7%; H, 6·9%; N, 5·3%; \( \text{C}_{15}\text{H}_{15}\text{NCl} \) requires C, 74·9%; H, 7·0%; N, 5·1%). The picrolonate of the above base was crystallised from alcohol when it was obtained as yellow needles melting at 109° (Found: C, 64·5%; H, 5·1%; N, 14·2%; \( \text{C}_{27}\text{H}_{28}\text{N}_{2}\text{O}_5 \) requires C, 64·8%; H, 5·2%; N, 14·0%).
N-β-phenethyl-a-picolinium bromide was obtained as colourless needles by crystallisation from alcohol and was found to melt at 108° (Found: N, 5·2%; C_{11}H_{16}NBr requires N, 5·0%). N-β-phenethyl-6-ethyl-picolinium bromide obtained by alkaline ferricyanide oxidation of the above quaternary salt and subsequent chromatographic fractionation of the oily material was a colourless crystalline solid. On recrystallisation from petroleum ether, it was obtained in the form of colourless plates melting at 108° (Found: C, 78·6%; H, 6·7%; N, 6·9%; C_{14}H_{13}NO requires C, 78·9%; H, 6·6%; N, 6·6%).

N-β-phenethyl-2-quinolone. The quaternary bromide formed between β-phenethyl bromide and quinoline could not be obtained in the form of a solid and the oily material as such was oxidised with alkaline ferricyanide. The product again was an oil which on chromatographic fractionation over alumina and recrystallisation from petroleum ether, was obtained in the form of colourless plates melting at 98° (Found: C, 81·8%; H, 5·9%; N, 6·0%; C_{12}H_{15}NO requires C, 81·9%; H, 6·0%; N, 5·8%).

N-β-(1-naphthyl) ethyl pyridinium bromide was obtained as colourless needles by crystallisation from alcohol. It melted at 110° (Found: N, 4·6%; C_{17}H_{15}NBr requires N, 4·5%). N-β-(1-naphthyl) ethyl pyridinium iodide was crystallised from alcohol when it separated in the form of colourless needles melting at 120° (Found: N, 4·0%; C_{17}H_{15}NI requires N, 3·9%; H, 6·0%).

N-β-(1-naphthyl) ethyl-2-pyridone. It was obtained as colourless plates by recrystallisation from alcohol. It melted at 72° (Found: C, 81·2%; H, 6·0%; N, 5·7%; C_{17}H_{15}NO requires C, 81·9%; H, 6·0%; N, 5·8%; C_{13}H_{13}NO requires C, 3·4%; H, 5·8%; C_{17}H_{15}NCl requires C, 49·4%; H, 4·8%; N, 3·4%); 3:4:5:6:7:8-hexahydropyridone-1:2:1′:2′-naphthoquinolinium bromide, obtained by the cyclization of the above pyridone, was recrystallised from aqueous alcohol when it separated as a fine white powder melting at 177° (Found: C, 49·2%; H, 4·4%; N, 3·7%; C_{17}H_{15}NCl requires C, 49·4%; H, 4·8%; N, 3·4%), 3:4:5:6:7:8-hexahydropyridone-1:2:1′:2′-naphthoquinolinium bromide was obtained by the catalytic reduction of the above iodide. It was an oil, treatment of which with hydrochloric acid gave the hydrochloride. The latter was recrystallised from water when it was obtained in the form of a fine white powder melting at 218° (Found: C, 78·1%; H, 6·3%; N, 4·8%; C_{21}H_{21}NCl requires C, 78·1%; H, 6·5%; N, 4·3%). The hexahydropyridone gave a crystalline picate which on recrystallisation from alcohol was obtained as yellow needles, melting at 157° (Found: C, 62·5%; H, 4·3%; N, 11·0%; C_{27}H_{23}N_{4}O_{7} requires C, 62·9%; H, 4·5%; N, 10·9%).

N-β-(1-naphthyl) ethyl isouquinolinium bromide was obtained as pale brown needles by crystallisation from absolute alcohol-ether mixture it
melted at 158° (Found: N, 3.9%; C₂₁H₁₈NBr requires N, 3.8%). N-β-(1-naphthyl) ethyl isoquinolinium iodide was obtained as yellow powder on recrystallisation from alcohol. It melted at 190° (Found: N, 3.5%; C₂₁H₁₈NI requires N, 3.4%).

N-β-(1-naphthyl) ethyl-1-isoquinolone was prepared by oxidation of the bromide with alkaline ferricyanide and was obtained as colourless plates by recrystallisation from alcohol. It melted at 97°. 7 g. of the bromide gave 4.3 g. of the isoquinolone (Found: C, 83.7%; H, 5.5%; N, 4.3%; C₂₁H₁₇NO requires C, 84.2%; H, 5.6%; N, 4.6%). 3:4-dihydro-9:10-dehydro-1:2:1′:2′-naptho-7:8-benzoquinolinizinium iodide was made by the cyclisation of the above isoquinolone. 2.6 g. of the iodide was obtained from 2 g. of the former. On recrystallisation from alcohol it separated as a yellow powder melting at 192° (Found: C, 61.4%; H, 3.8%; N, 3.7%; C₂₁H₁₆NI requires C, 61.6%; H, 3.9%; N, 3.4%).

3:4:5:6-tetrahydro-1:2:1′:2′-naptho-7:8-benzoquinolizine was obtained by the catalytic reduction of the above base and subsequent chromatographic fractionation of the oil got. It was recrystallised from alcohol when it separated as colourless white plates melting at 98° (Found: C, 88.5%; H, 7.2%; N, 5.1%; C₂₁H₂₀N requires C, 88.1%; H, 7.0%; N, 4.9%). The picrate of the above base on recrystallisation from alcohol was obtained as a yellow powder melting at 209° (Found: C, 63.2%; H, 4.7%; N, 11.1%; C₂₇H₂₅N₄O requires C, 62.9%; H, 4.5%; N, 10.9%). The picromulate of the base was crystallised from alcohol and was obtained as a yellow powdery solid melting at 190° (Found: C, 67.4%; H, 5.3%; N, 12.9%; C₃₁H₂₉N₃O₅ requires C, 67.6%; H, 5.1%; N, 12.7%).

N-β-(1-naphthyl) ethyl quinininium bromide was obtained as a colourless powdery solid on recrystallisation from water. It melted at 172° (Found: N, 3.7%; C₂₁H₁₈NBr requires N, 3.8%). N-β-(1-naphthyl) ethyl quinininium iodide prepared from the above bromide was recrystallised from alcohol when it separated in the form of fine needles, melting at 204° (Found: N, 3.5%; C₂₁H₁₈NI requires N, 3.4%). N-β-(1-naphthyl) ethyl-2-quinolone obtained by the oxidation of the bromide was crystallised from dilute alcohol when it separated in the form of pale brown flakes melting at 172° (Found: C, 83.9%; H, 5.6%; N, 4.3%; C₂₁H₁₇NO requires C, 84.3%; H, 5.7%; N, 4.7%).

3:4-dihydro-9:10-dehydro-1:2:1′:2′-naptho-5:6-benzoquinolinizinium iodide, the product obtained on cyclisation of the above quinolone was crystallised from alcohol when it was got as a yellow powdery solid melting at 193° (Found: C, 61.4%; H, 3.8%; N, 3.6%; C₂₁H₁₆NI requires C, 61.6%; H, 3.9%; N, 3.4%).
3: 4: 7: 8-tetrahydro-1: 2: 1': 2' naphtho-5: 6: 1: 2' benzoquinolizine was obtained by the reduction of the foregoing nodule and on recrystallisation from alcohol after chromatographic purification it separated in the form of yellow needles melting at 111° (Found: C, 88·2°; H, 7·5°; N, 4·9°; C_{17}H_{14}N requires C, 88·0°; H, 7·4°; N, 4·7°.) The picrate of the above base prepared in the usual way was crystallised from alcohol when it was separated as yellow needles melting at 145° (Found: C, 63·8°; H, 4·5°; N, 10·7°; C_{22}H_{18}N requires C, 63·5°; H, 4·5°; N, 10·5°).

N-β-(1-naphthyl) ethyl-4-methyl quinolinium bromide was crystallised from absolute alcohol-ether when it separated in the form of shining plates melting at 196° (Found: N, 3·9°; C_{22}H_{19}NBr requires N, 3·9°.)

N-β-(1-naphthyl) ethyl-4-methyl-2-quinolone obtained by the oxidation of the above bromide was an oil which on chromatographic fractionation gave a crystalline solid. The latter on recrystallisation from petroleum ether was obtained as a colourless powder melting at 98° (Found: C, 84·1°; H, 6·1°; N, 4·7°; C_{22}H_{19}NO requires C, 84·3°; H, 6·1°; N, 4·5°.)
SUMMARY

The scope of the Sugawara method for the synthesis of quinolizinium derivatives has been investigated. Several benzo, naphtho and naphtho-benzo quinolizinium compounds have been synthesised in excellent yields, although the rule on which evolvsion was effected did not carry any activating substituents.

REFERENCES

1. Sugawara and Sagara, Rec., 1949, 72, 977.